REMARKS

1. Claim Status

Method claims 39-76 remain pending in the application. Claims 39-75 were finally rejected in the September 1, 2010 Office Action. Claim 76 is new. Support for new claim 76 can be found throughout the originally filed specification, examples and claims. No new matter has been added by way of the present amendment.

Applicant respectfully requests that the method claim amendments presented herein be entered in the application as they place the application in a condition for allowance. Applicant maintains for the reasons explained below that method claims 39-76 as presented herein are allowable and should be passed to issue. Applicant addresses each of the Examiner's previous concerns in the sections which are presented hereinbelow.

Applicant wishes to request an interview with Examiner Badio before the issuance of a first office action and anticipates that the first action, if not a notice of allowance, will be a ***non-final*** first office action. If Examiner Badio believes that the first office action should be a final office action, she is cordially requested to telephone the undersigned attorney and give the attorney ample time to file an amendment of the claimed invention to further define the invention and file a further amendment.

2. Claims 57-64 Satisfy the Written Description Requirement

In the September 1, 2011 Office Action, the Examiner maintained her rejection of claims 57-64 under 35 U.S.C. § 112,¶ 1 for failure to satisfy written description on grounds that the specification of the application as originally filed, when coupled with the knowledge of those of ordinary skill in the art as of the filing date, did not support a claim to "reducing the likelihood of a recurrence of breast cancer". Applicant traverses

these rejections and respectfully maintains that claims 57-64 satisfy written description for the following reasons.

Claim 57 as drafted is directed to a method of reducing the likelihood of a recurrence of estrogen-sensitive breast cancer in a patient. This clause is expressed distinctly in the specification and in particular, in the second full paragraph on page 3. It is unequivocal that the specification supports claim 57 and in particular, the use of the language "reducing the likelihood of a recurrence of breast cancer". Apparently, this simple and incredibly straight forward concept and statement which virtually *anyone* of ordinary skill in the art could readily understand and practice somehow contravenes the written description requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the Examiner's rejection for the following reasons and respectfully request that the Examiner withdraw this rejection for the reasons presented herein.

The first paragraph of 35 U.S.C. §112 requires that the specification shall contain a written description of the invention (as per the Examiner) "to clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed" (see pages 2-3 of the September 1, 2011 office action). To paraphrase, the relevant inquiry is whether the present specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Applicant respectfully submits that he unequivocally described the invention of claim 57 (and the claims decpendent thereon) in the original specification and one of ordinary skill could readily understand the description of that invention from a reading of the original application.

Claim 57 is a rather straight-forward claim which is directed to a "method of reducing the likelihood of a recurrence of estrogen-sensitive breast cancer in a patient comprising administering to said patient an effective amount of a selective estrogen receptor modulator (SERM) which has the chemical structure..." as set forth in the claim. This claim clearly and specifically is directed to a method to reduce the likelihood of the

recurrence of breast cancer in a patient by administering one or more of the compounds set forth therein.

The term *recurrence of cancer* is defined rather simply by the American Society of Clinical Oncology as follows:

A "recurrence is when the cancer comes back after treatment."

The passage goes on to say: "The ultimate goal of any cancer treatment is to remove or destroy all of the cancer cells in the body. When cancer cells can no longer be found in the body, a cancer is considered to be in remission, meaning the disease is temporarily or permanently gone. A recurrence is when the cancer comes back after remission. Cancer recurs because small areas of cancer cells are difficult to find and can sometimes remain in the body after treatment. Over time, these cells may multiply and grow large enough to be found and diagnosed. Depending on the type of cancer, this can happen in weeks, months, or even many years after the primary (original) cancer was treated." See the definition and passage at the following url: **http://tinyurl.com/45mlpwb**.

A similar definition of "recurrence of breast cancer" may be found at the following url: **http://tinyurl.com/4uc7sfo** .

"After a remission of cancer, if signs or symptoms of cancer reappear, that is called a "recurrence," where cancer cells can reappear in the site of the primary tumor or can show up in a new location. Also known as a relapse, return or reappearance."

Applicant respectfully submits that the person of ordinary skill, the clinical oncologist can readily understand claims 57-64 and recognize precisely and exactly the nature of the invention which Applicant has claimed.

The Examiner's argument on page 3 of the office action with respect to biological activity of the chemically unrelated, but known SERMS tamoxifen and raloxifene (which exhibit similar activity to the compounds of the present invention) is misdirected, inasmuch as the Examiner's argument appears to be directed to the question of whether Applicant's method claims of 57-64 is effective, given the prophylactic nature of the claim, not whether or not Applicant described the rather simple method of reducing the likelihood of a breast cancer recurrence by administering a compound which is described quite clearly in the claim. To that end, Applicant references the two previously submitted peer-reviewed and published papers by Applicant Professor Richard Hochberg, *J. Clin. Endocrinol. Metab.*, July 2004, 89, pp. 3527-3535 and *J. Med. Chem.*, 2005, 48, 1428-1447 (copies enclosed), which clearly evidence that the steroidal compounds which are set forth in the claims of the present application exhibit unequivocal Selective Estrogen Receptor Modulation (SERM) activity (i.e., estrogenic activity in the liver and skeleton and anti-estrogenic activity in the uterus and breast tissue) similar to the activity which is exhibited by the clinically used SERMs tamoxiphen and raloxifene and may be used analogously.

In the present application, Applicant clearly provides sufficient description of the invention to convey to those of ordinary skill (a skilled oncologist treating breast cancer patients) that the compounds as claimed could be used in a method to inhibit or reduce the likelihood that breast cancer will recur in a patient. Given the years of experience of practitioners with compounds of similar activity such as tamoxifen and/or ramoxifene in reducing the likelihood of breast cancer recurrence using these SERM agents and the wealth of experience of clinical oncologists in treating breast cancer, a method of using the steroidal SERMs of the present invention to reduce the likelihood of breast cancer recurrence in a patient is fully described and adequately conveyed. This is further supported by the previously submitted declaration of Dr. Richard Hochberg, in paragraph 14.

Accordingly, Applicant maintains that claims 57-64 clearly satisfy the written description requirement and respectfully request the Examiner withdraw her rejection of claims 57-64 on these grounds.

3. Claims 39-75 Are Nonobvious Over the Teachings of van den Broek

In the September 1, 2010 Office Action, the Examiner had rejected of claims 39-75 under 35 U.S.C. § 103(a) as being unpatentable for obviousness over U.S. Patent No. 3,972,906 ("*van den Broek*").

According to the Examiner, at the time of the invention of the pending claims, the use of *van den Broek's* estrogenic compounds to treat menopausal symptoms and breast cancer would have been obvious. Essentially, the Examiner argues that "the issue is not whether the art recognized the differences in the action of the compounds in different target organs. The issue is whether the art teaches or suggests the use of the compounds as claimed by the instant invention."

Applicant agrees with the Examiner in her characterization of the issue of obviousness/non-obviousness to be resolved, but notes that Van den Broek's teachings are such that they would not given rise to the currently claimed methods and are, in fact, incompatible with the *method* claims of the present invention. This is based upon Applicant's discovery that the compounds which are set forth in the present *method* claims exhibit unexpected selective estrogen receptor modulating (SERM) activity which are used in methods which make use of that unexpected activity *to the exclusion of the activity which is taught by van den Broeck.* Thus, the presently claimed methods are directed to uses of compounds which rely on the activity which could not be surmised or determined from the teachings of van den Broeck. It is Applicant's view that the currently claimed methods are non-obvious over the teachings of van den Broeck.

Thus, Applicant respectfully contends that the compounds set forth in the present *method* claims evidence unexpected activity as selective estrogen receptor modulators (SERMs) and this unexpected activity, which was completely unrecognized by and non-obvious over the teachings of van den Broek, provides claimed methods which are clearly non-obvious, patentable and distinguishable over the teachings of van den Broek, which issued in 1976[2].

Applicant's claimed methods represent the first use of steroidal SERM's:
(a) to treat the menopausal symptoms as claimed in a patient while reducing the risk that the patient develops, or experiences a recurrence of, an estrogen-sensitive cancer;
(b) to treat an estrogen-sensitive cancer;
(c) to reduce the likelihood of a reoccurrence of breast cancer in a patient, and
(d) to treat the symptomology of menopause as claimed in a patient suffering from an estrogen-sensitive cancer.

All of the claimed methods rely on SERM activity (i.e., the unexpected combined estrogenic/anti-estrogenic activity) for the claimed methods and distinguish over the teachings of van den Broek based upon this unexpected SERM activity. Contrary to the Examiner's contention, the skilled practitioner, based upon the teachings of van den Broeck would not have recognized the activity of the present compounds as SERMS, and would, therefore, not use the present compounds (even if taught by van den Broeck) in the methods of the present invention. The present invention thus represents new uses of old compounds (as described by the Examiner).[3]

At the time of the invention of the pending claims, the non-steroidal SERM Tamoxifen® was indicated for the treatment and prevention of breast cancer. It was

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[2] Applicant points out the issue date of van den Broek only to emphasize the point that if van den Broek had taught or suggested the present invention as the Examiner argues, surely one of ordinary skill would have discovered the highly desirable SERM activity of the putatively disclosed compounds of van den Broek well before Applicant's invention in 2002, some *twenty-six* years later.

[3] Applicant maintains that pharmaceutical compositions which are based upon the compounds set forth, but not claimed in the present application, are patentable over the art of record, but those arguments are to be presented in any divisional application claiming those compositions, if applicable.

recognized that post-menopausal patients treated with Tamoxifen® could benefit from a potential reduction in bone loss and cholesterol levels. Also, at the time of the invention of the present application, the use of steroidal estrogen receptor ***agonists*** such as those disclosed by the art of record (van den Broek) to treat post-menopausal symptoms were associated with an enhanced risk of breast cancer in that therapy and ***contraindicated*** for those reasons. The present invention addresses the concerns of the art with the unexpected discovery that *steroidal* compounds which are presently set forth in the method claims of the present invention exhibit unexpected SERM activity and the presently claimed methods make use of that unexpected activity to the exclusion of the prior art teachings.

Applicant respectfully submits that van den Broek does not teach or suggest that *any* of the compounds which are disclosed therein exhibit selective estrogen receptor modulator (SERM) activity as in the present invention. Instead, van den Broek teaches a myriad number of compounds which exhibit a broad range of activities which include contraceptive, estrogenic, progestational, ovulation-inhibiting, gonad-inhibiting and anabolic properties. Van den Broek is primarily directed to chemical compounds and the disclosure set forth in that reference is almost exclusively devoted to chemical compounds and chemical synthesis of those compounds. There is absolutely ***no*** biological activity of *any* of the compounds which are set forth in the present claims. None of the biological activity of the presently claimed compounds is exemplified and presented in van den Broek. ***None.*** Thus, with respect to the biological activity of the present compounds putatively disclosed in van den Broeck, that activity must be described as, at best, *prophetic*, and more accurately, as non-disclosed. That is, if one of ordinary skill wanted to identify the biological activity of a number of the compounds which are set forth in the presently claimed invention and which (as the Examiner contends) are putatively disclosed in van den Broek[4], that person of ordinary skill would

[4] Applicant maintains that van den Broek does not disclose the presently claimed compounds and to the extent that one of ordinary skill might surmise that the presently claimed compounds might exhibit estrogen agonist activity, that person of ordinary skill would be disabused from such a teaching after those putative compounds were actually made and tested and exhibited anti-estrogenic activity in the relevant assays.

have to make the compounds and test the compound's activity only to find the compounds did *not* possess the activity desired by van Broek (estrogen agonist activity) in the relevant assays.

With respect to the suggested estrogenic activities of the van den Broek compounds, the only activity disclosed or suggested therein which is even relevant to the question of patentability of the present invention appears in column 2, lines 28-48, where van den Broeck discloses that certain 11β-substituted steroidal compounds exhibit estrogenic (agonist) properties. In particular, van den Broek cites a number of specific compounds with different pharmacophores as exhibiting estrogenic activity. However, the ***only*** specifically disclosed compounds relevant to the present invention and having a similar estradiol pharmacophore to those used in the present invention are 11*β*-methoxymethyl-ethinyl-estradiol and 11*β*-chloromethyl-ethinyl-estradiol. In particular, these estradiol compounds of van den Broek have a methoxymethyl group or a chloromethyl group at the 11β position of estradiol and an ethinyl group at the 17 position of estradiol. See, van den Broek, column 2, lines 28-48. It is noted that every compound which is *specifically* disclosed by van den Broek as having estrogenic (agonist) activity has a *short-chain group* at the 11β position of the steroidal pharmacophore, i.e., a chain-length of 3 (methoxymethyl) or 2 (chloromethyl) non-hydrogen atoms, regardless of pharmacophore. None of the other compounds is specifically disclosed in van den Broek as having estrogenic activity.

The biological activity (estrogen agonist activity) suggested in van den Broek for the disclosed short-chain 11β substituents (methoxymethyl or chloromethyl) is corroborated by the experiments presented on pages 22-25 of the present application. Indeed, a review of the structure activity relationship related to 11β substituents of estradiol in the present application (see especially tables 1 and 2 on pages 23 and 24) evidences that the short-chain compounds which are *specifically* disclosed by van den Broek do *indeed* exhibit estrogenic activity, but when the 11β side-chain is lengthened to 5 or more non-hydrogen atoms as presently claimed, the compounds become ***anti-***

estrogenic exhibiting SERM activity, an unexpected result, and a result which stands in complete contrast to the biological activity of the compounds disclosed by van den Broek. The compounds of the present invention exhibit *anti-estrogenic* activity consistent with their activity as SERMS, not estrogen agonists, as taught and required by van den Broek. Van den Broek does not disclose or suggest the pharmacological activity (SERM) of the presently claimed compounds. Given the clear deficiency of van den Broek, van den Broek clearly does not disclose or suggest the methods of the present invention which rely on the unexpected (and non-disclosed by van den Broeck) SERM activity of the claimed compounds in order to practice the presently claimed methods, which are completely distinguishable from the prior art teachings of van den Broeck. Moreover, the compounds which are set forth in the present method claims would not be used as estrogen agonists, because they do not have/exhibit estrogen activity consistent with the teachings of compounds of van den Broek.

It is respectfully submitted that the estrogenic compounds which are disclosed by van den Broek are *contraindicated* for use in the presently claimed methods and consequently, van den Broeck *teaches away* from the present invention. For example, each of the methods which are presented in independent claims 39, 48, 57 and 65 rely on the unexpected SERM activity of the claimed compounds in order to effectively and favorably practice the claimed invention. Noting that estrogen agonists are *contraindicated* in patients with or at risk for estrogen-sensitive cancer such as breast cancer, and estrogen agonists *worsen*, rather than *treat*, these cancers, the present compounds, which are anti-estrogenic in those tissues where estrogen-sensitive cancers develop, provide meaningful utility and benefit in the methods of the present invention, in complete contrast to the teachings of van den Broek, which do not. Moreover, following the teachings of van den Broek would *never* result in the present invention.

The presently pending claims make use of the unexpected activity exhibited by the claimed compounds. Thus, in claim 39, which is directed to a method for treating menopause while reducing the risk that a patient will develop an estrogen-sensitive

cancer, the SERM compounds as claimed are particularly useful because they are effective against estrogen-sensitive cancer, whereas the van den Broek estrogenic compounds are *contraindicated* because estrogen agonists actually *increase* the risk of estrogen-sensitive cancers. In claim 48, which is directed to treating an estrogen-sensitive cancer in a patient, treatment is favorably provided by the SERM compounds of the present application because of the unexpected anti-estrogenic activity displayed, whereas the van den Broek estrogenic compounds are *contraindicated* (see the discussion below and the previously submitted declaration of Dr. Richard Hochberg, in paragraph 12). In claim 57, which is directed to reducing the likelihood of a recurrence of breast cancer (an estrogen-sensitive cancer), the compounds of the present invention, because of their unexpected SERM activity, find favorable use, whereas, the van den Broek estrogen agonist compounds are again *contraindicated.* Likewise, in claim 65, which is directed to a method for treating menopause in a patient with an estrogen-sensitive cancer, the compounds according to the present invention exhibit favorable activity in treating the symptomology of menopause without exacerbating estrogen-sensitive cancers (because they are estrogen *antagonists* in estrogen-sensitive tissues), whereas the van den Broek compounds are contraindicated for the method of claim 65 because of the disclosed estrogenic agonist activity, which exacerbates/worsens estrogen-sensitive cancer and is contraindicated in estrogen-sensitive cancer. The same is true for all of the remaining claims, which are dependent on claims 39, 48, 57 and 65.

Thus, contrary to the Examiner's contention, the compounds which are presented in the pending method claims exhibit unexpected activity when used in the pending methods and this unexpected activity and the pending methods are not taught or suggested by van den Broek. As explained, van den Broek actually *teaches away* from the present method claims inasmuch as the biological activity which is taught by van den Broeck is *contraindicated* in the claimed methods. There can be no greater evidence of non-obviousness over a reference than when that reference, when used within the context of its teachings, teaches something which should be avoided.

In short, the presently claimed methods deviate from the prior art precisely at the point of invention where the present invention is favorably used because of the unexpected biological activity (SERM) exhibited by the claimed compounds, whereas the compounds of the prior art are actually contraindicated. The Examiner's argument that the compounds disclosed by van den Broek would *inherently* produce the claimed methods is not credible, given that the compounds which are claimed in the present methods are *not* specifically disclosed by van den Broek, and if one were to *theoretically* make compounds according to the present invention and test those compounds in a traditional estrogen assay (see the previously submitted May 2, 2007 declaration of Richard Hochberg, and in particular at paragraph 19), that person of ordinary skill would have realized that the compounds had no art recognized estrogen agonist activity. The person of ordinary skill would have concluded that the compounds set forth in the presently claimed *method* claims, in essence, are essentially *useless* for the purposes for which estrogen agonist compounds are taught in van den Broek.

Applicant further submits that the presently claimed compounds as having SERM activity are not taught by van den Broek and one of ordinary skill would not have been motivated to make and use the present compounds in the presently claimed *methods* which rely on SERM activity, given the teachings of van den Broek. Applicants respectfully submit that the compounds according to the present invention, which exhibit anti-estrogenic activity in traditional estrogen receptor models (see paragraphs 14-22 of the previously submitted declaration of Dr. Richard Hochberg dated May 2, 2007, previously enclosed) would not have been considered useful by van den Broek for treating menopause, because menopause treatment traditionally required estrogen agonist activity in the vagina and uterus, to address vaginal dryness and hot flushes, whereas the present compounds, are anti-estrogenic in the vagina and uterus. Thus, the unexpected SERM activity which is exhibited by the present compounds stands in complete contrast to the desired activity (estrogenic agonist) of van den Broek and would not be considered appropriate. Moreover, van den Broek does not disclose SERM activity of any of the

disclosed compounds. It is certainly not obvious to use a compound whose activity is not known in a method which requires that activity.

Based on what was known in the prior art and their own knowledge, those of ordinary skill in the art at the time of the invention of the pending claims would have reasonably believed that the presently claimed SERM compounds would have failed to achieve the purposes of the van den Broek taught methods *and* separately, the purpose for which the currently claimed methods are applied, precisely because of the unknown and unexpected (SERM) activity exhibited by the presently claimed compounds. *See Takeda Chem. Indust. v. Alpharma Pty Ltd.*, 492 F.3d 1350; 2007 U.S. App. LEXIS 15349; 83 U.S.P.Q.2D (BNA) 1169 (Fed. Cir. 2007), *cert. denied*, 2008 U.S. LEXIS 3015 (U.S., Mar. 31, 2008).

Regarding the Examiner's arguments that a compound and its properties are not separable, Applicants merely point out that while that basic tenet is true, the actual compounds used in the present invention exhibit substantially different and unexpected pharmacological activity from the compounds taught by van den Broek and the methods of the present invention make use of these activity differences between the compounds used in the present invention and the prior art taught compounds. While it is true that one cannot separate a compound from its properties, where, as here, the properties of the compounds deviate from the teachings of the prior art and Applicant makes (new) use of those newly discovered properties in a way that clearly relies on and distinguishes that unexpected activity from the teachings of the prior art, invention ***exists***. This is well settled law. See, *inter alia*, *In re Thuau*, 30 C.C.P.A. (Patents) 979 (1943), 135 F.2d 344, 57 U.S.P.Q. 324, amongst a long line of cases addressing the same point. See also *In re Figgins*, 397 F.2d 356, footnote 4: "In such eventuality, appellant's discovery of the analgesic properties of "O_2" and of a composition containing it could properly be claimed only as a method or process of using that compound or composition in accordance with the provisions of 35 U.S.C. §§ 100(b) and 101. In re Hack, 245 F.2d 246, 44 CCPA 954 (1957); In re Thuau, 135 F.2d 344, 30 CCPA 979 (1943), and cases cited therein."

The Examiner appears to be confusing the impact of van den Broeck's teachings on compound claims in general (which are not pending) and the method claims of the present application, which rely on patentability by making use of the newly discovered activity of compounds in a way not taught or suggested by the prior art.

It is Applicant's further respectful position that the Examiner's obviousness rejection ignores both the purposes for which the claimed methods are administered and the advantages of those methods, and further presupposes knowledge on the part of skilled artisans about the nature and properties of the administered compounds that could have only been gained from Applicant's invention. Van den Boerk clearly did not disclose SERM activity for any disclosed compound, let alone compounds used in the present invention. Such a hindsight reconstruction of the prior art is legally impermissible. *See Ortho-McNeil Pharma., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 86 U.S.P.Q.2d 1196 (Fed. Cir. 2008) (*KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness; only by impermissible hindsight could patentee's selection and modification of a compound putatively developed for a different application be found obvious in this instance).

The Examiner's reliance on the doctrine of inherency in asserting the obviousness of the present invention based upon van den Broeck is misplaced given that the person of ordinary skill would first have to recognize the inherent activity of the compounds which are presently claimed before using the compounds in methods which rely on those inherent characteristics as in the present invention. Without recognizing that activity, use in the present invention is *avoided*. The point is that van den Broeck emphasizes the desirability of *estrogen agonist* activity and requires such activity, whereas the present compounds exhibit anti-estogenic activity in precisely those assays van den Broeck relied upon to establish estrogen activity and rely on that (unrecognized by van den Broeck) anti-estrogen activity to provide the favorable results in the methods of the present invention.

Accordingly, Applicant maintains that claims 39-75 are clearly nonobvious over van den Broek.

4. Claims 39-75 Are Nonobvious Over the Teachings of van den Broek, in view of Cameron, Palkowitz and Bodor

The Examiner has rejected claims 39-75 under 35 U.S.C. §103(a) as being unpatentable over van den Broek, in view of Cameron, U.S. patent publication no. 2001/0025051 ("Cameron"), Palkowitz, U.S. patent no. 6,268,361 ("Palkowitz") and Bodor, et al., U.S. patent no. 4,617,298 ("Bodor") for the reasons which are set forth in the September 1, 2010 office action on pages 7-8. Essentially, the Examiner argues that because estrogen was known to be used to treat "estrogen-sensitive" cancer, as well as the symptoms of menopause, it would have been obvious to the skilled artisan to treat estrogen-deficiency syndromes such as menopausal symptoms, osteoporosis and estrogen-dependent cancer using the compounds as taught by van den Broek. The Examiner further argues that the treatment which is taught by van den Broek, inherently results in the presently claimed methods. Applicants respectfully traverse the Examiner's rejection for the following reasons.

The teachings of van den Broek and the failure of the prior art to recognize the existence of SERM activity in any of the compounds disclosed therein, or the benefits that SERM activity provides in relationship to the claimed methods, discussed in detail hereinabove, is referenced here. In essence, van den Broek failed to teach the unexpected pharmacological activity of the presently claimed compounds which are used in methods according to the present invention which rely on that activity, and the known pharmacological activity as taught by van den Broek is *contraindicated* for use in the presently claimed methods. It is the clearly distinguishable and unexpected SERM activity of the compounds as presently claimed in methods which rely on and distinguish over the prior art estrogen agonist compounds based upon that unexpected activity which forms the basis and foundation of the patentability of the present invention.

Van den Broek does not disclose or suggest the present invention for the reasons which are presented hereinabove. None of Cameron, Palkowitz or Bodor, taken alone or in any combination, cures the deficiencies of van den Broek in failing to suggest the present invention. Much of the disclosure of Cameron, Palkowitz and/or Bodor is actually irrelevant to the present invention, because the compounds and pharmacophores disclosed in each of those references are simply unrelated to the present invention. The more generic disclosure of those references upon which the Examiner relies, as to the use of estrogen agonists in the treatment of estrogen-sensitive cancers, actually *supports* the non-obviousness and patentability of the present invention, rather than rendering the present invention obvious. Thus, the prior art relied on by the Examiner again, *teaches away* from the present invention. Applicant notes again that the present claims are directed to ***methods*** which use compounds which are undisclosed by van den Broeck as possessing SERM activity and utilize the unexpected activity of these compounds in these ***methods*** which produce results which rely on that unexpected activity in complete contravention to the teachings of van den Broeck.

Cameron is directed to certain compounds for preventing breast cancer. These compounds, which are completely unrelated structurally to the present invention, are said to be useful for preventing breast cancer. The teachings of Cameron have little to do with the present invention other than to point out that estrogen agonists have been used in combination with other agents in the treatment of *prostatic* cancer (paragraph 003), which is an androgen sensitive cancer, and are *contraindicated* for use in the treatment of estrogen-sensitive cancers, including breast and endometrial cancer (paragraph 008). Notwithstanding the Examiner's reliance on the teachings of Cameron, those teachings actually emphasize the patentability of the present invention and support Applicant's point- that compounds which have SERM activity (i.e., those used in the present invention) are favorably used in the present methods, whereas the prior art estrogen agonist compounds (such as those taught by van den Broek) are actually contraindicated for use in the present invention. Cameron teaches the person of ordinary skill to *avoid*

estrogen agonists and to favorably use SERMS in breast cancer and uterine cancer, the precise support for patentability that Applicant relies on. However, Cameron suggests nothing with respect to any compound disclosed in van den Broek or ***any*** steroidal compound for that matter, and no such conclusion or inference could be drawn about the compounds used in the present invention from Cameron. Cameron, contrary to rendering the present invention obvious, actually *supports* the patentability of the present invention.

Turning to the teachings of Palkowitz, this reference is relevant in that it, like Cameron, also teaches that the use of estrogen agonists in treating estrogen-sensitive (estrogen-dependent) cancers is contraindicated and to be avoided (column 2, lines 40-57). Palkowitz is otherwise related to naphthyl compounds which are completely unrelated to the chemical structures of the compounds used in the present invention (steroidal pharmacophore). Just as Cameron could be seen by one of ordinary skill in the art as *supporting* Applicant's claim for patentability, rather than the Examiner's position, so too does Palkowitz support the patentability of Applicant's invention. In short, Palkowitz does nothing to obviate the deficiencies of the teachings of van den Broek and Cameron in failing to suggest the present invention. In fact, Palkowitz does quite the opposite.

Regarding the teachings of Bodor, this reference is directed to a number of compounds which are principally directed to certain salts of steroids having estrogenic activity which are used to enhance weight control activity. None of the compounds which are disclosed therein are related to the present invention and none of the compounds disclosed therein or the disclosure provided, even allude to the compounds and methods of the present invention. Bodor, in the background of the invention section, does make an oblique reference to the use of estrogen compounds in the treatment of breast cancer, but otherwise does not provide any disclosure which is even relevant to the present invention. It is noted that estrogen agonists actually are contraindicated for use in the treatment of estrogen-sensitive cancers (see the previously submitted declaration of Dr. Richard Hochberg), and although estrogen agonists historically were used in

combination with other agents to treat cancer, that approach has been discontinued because of the tendency of that therapy to *exacerbate or worsen* the estrogen-sensitive cancer. Thus, the much earlier published Bodor must also be read in conjunction or combination with the more contemporary Cameron and Palkowitz as supporting the relevance and benefit of the present invention. Bodor, in essence, does essentially nothing to cure the deficiencies of the other art in failing to suggest the present invention.

Note that with respect to the present invention, the compounds which are presently claimed in the methods of the present invention do not exhibit favorable activity as estrogen agonists and are otherwise known as anti-estrogens. So, even if Bodor's 1986 disclosure is read in isolation (i.e., without reference to the later published Cameron and/or Palkowitz) in combination with van den Broek, and estrogen agonists are suggested for treating breast cancer (an approach which is actually counterproductive and deleterious to the breast cancer therapy outcome- see the previously submitted declaration of Richard Hochberg), the present compounds would not be used pursuant to those teachings because, as explained hereinabove, the present compounds *do not* exhibit estrogen agonist activity as called for by the Bodor treatment and as taught by van den Broek. Applying Bodor to the teachings of van den Broek (in the absence of Cameron and/or Palkowitz) would result in the *avoidance* of the present method to use the compounds as claimed as estrogen agonists in treating cancer (as erroneously taught by Bodor), because the compounds in the presently claimed methods would have been shown to exhibit *anti-estrogen activity* in the relevant assays, not the required (as taught by Bodor) estrogen agonist activity, thus ***avoiding*** the present methods.

The position of the Examiner that it would have been obvious to use the presently claimed SERM compounds for the treatment of estrogen-dependent cancer because the prior art teachings suggest the use of the van den Broek estrogen agonist compounds for the treatment of estrogen-sensitive cancers as taught by Cameron, Palkowitz and Bodor is simply not credible. As discussed above, the person of ordinary skill would not have recognized, from van den Broek, the SERM activity of the present invention, which is

favorably used in the presently claimed ***methods*** . Whether one relies on the combined teachings of van den Broek and Bodor or the combined teachings of van den Broek and Bodor with either one or both of Cameron and Palkowitz, one never provides the present invention, given that van den Broek and Bodor together rely on estrogen agonist activity which is not even present in the compounds used in the present invention. Reliance on van den Broek and Bodor, in combination with the teachings of Cameron and Palkowitz is misplaced and further confuses the teachings, given that the teachings of Cameron and Palkowitz, significantly more contemporary than Bodor, completely contradict the teachings of Bodor and lead the person of skill away from using the estrogen agonists of van den Broek in the present invention.

In sum, the person of ordinary skill would not have used the presently claimed compounds in methods requiring estrogenic agonist activity (Bodor) because the anti-estrogenic activity of the presently claimed compounds is actually *inconsistent* with the requirement for estrogenic agonist activity as taught by van den Broek and Bodor (despite the fact that the suggested method was later shown to be ineffective and/or deleterious). If one were to rely on Cameron and Palkowitz, alone or in combination with Bodor, these references would not cure the deficiencies of van den Brock- they would actually point out the fallacy and inadequacy of using the van den Broek disclosed compounds to treat estrogen sensitive cancer as taught by Bodor. In either instance, if analyzed correctly, one of ordinary skill would not have recognized the SERM activity of the presently claimed compounds because that activity was not even obliquely mentioned by van den Broek, or any of Cameron, Palkowitz and/or Bodor. It was not until the present application that the SERM activity of the presently claimed compounds became known and the benefit of such activity in the methods of the present invention which rely on that activity could have been realized.

As a separate note, contrary to the Examiner's contention, the presently claimed invention is not inherent to the disclosure of the prior art references, because, as explained, the person of ordinary skill would not have even used the presently claimed

compounds because they were not suggested for use as SERMS and would not have the requisite activity (as estrogen agonists) as taught by van den Broek. The Examiner's reliance on the doctrine of inherency here is not cogent inasmuch as the doctrine of inherency requires the inevitability of the claimed method occurring as a consequence of practicing the invention which is disclosed, and there is simply no disclosure in van den Broek or in any of Cameron, Palkowitz and/or Bodor which inevitably points to the use of the presently claimed compounds in the present methods. The use of the specifically disclosed estrogen agonist compounds of van den Broek, required by a cogent inherency analysis, would clearly not result in the present invention, given that the present compounds do not competently exhibit estrogen agonist activity in those assays relied upon by van den Broek. Contrary to the Examiner's position, Applicant has not merely identified or even used inherent aspects of methods of treatment disclosed or otherwise suggested by *van den Broek* or the other references. In particular, discovering and using unidentified synthetic steroids possessing SERM activity for the purposes for which Applicant's claimed methods are administered was not suggested by, and in fact was contrary to, the teachings of the art.

Indeed, the present methods are not even accidentally practiced by relying on the teachings of the prior art given that van den Broek and Bodor teach the requirement for estrogen agonist activity (which the presently claimed SERM compounds do not possess) and the remaining teachings of Cameron and Palkowitz teach that the use of estrogen agonists should not even be used in the first place. The Examiner's reliance on the doctrine of inherency here is respectfully, misplaced. *Cf. Rapoport v. Dement, et al.*, 254 F.3d 1053, 1059, 59 U.S.P.Q. 2d 1215 (Fed. Cir. 2001).

It is respectfully submitted that the presently claimed invention is patentable. The unexpected activity of the claimed compounds as SERMS is neither disclosed nor suggested by the art of record and this unexpected activity has been put to use in claimed methods which clearly rely on and distinguish over the art based upon this unexpected activity.

Given what was known in the prior art and their own knowledge, those of ordinary skill in the art at the time of the invention of the pending claims in the present methods would have reasonably believed that the presently claimed compounds would have failed to achieve the purposes of the prior art taught methods *and* the purpose for which the currently claimed methods are applied. *See Takeda Chem. Indust. v. Alpharma Pty Ltd.*, 492 F.3d 1350; 2007 U.S. App. LEXIS 15349; 83 U.S.P.Q.2D (BNA) 1169 (Fed. Cir. 2007), *cert. denied*, 2008 U.S. LEXIS 3015 (U.S., Mar. 31, 2008). The present invention is clearly patentable over the disclosed prior art.

As a final note regarding the Examiner's discussion of the previously submitted declaration of Dr. Richard Hochberg on page 8 of the office action, Applicant wishes to point out that the discussion of SERM activity by Dr. Hochberg related to the point that the compounds which appear in the present *method* claims exhibit activity which was unknown and undisclosed by van den Broek. The Examiner continues to argue about the discovery of an unappreciated property of a prior art compound or compound as being irrelevant to patentability. While the substance of the Examiner's argument in this regard would be accurate if the claims were directed to ***compounds or compositions***, such substance is not accurate as it relates to the presently pending ***method*** claims (no compound/composition claims are presently pending). It is well settled law that a new use of an old composition or compound is patentable where, as here, the new use is directed to a method which is patentably distinguishable over the teachings of the art. Notwithstanding the fact that Applicants strongly believe that van den Broek does not teach the present compounds, either literally or inherently, such a discussion is irrelevant to the issue which the Examiner continues to rely on to reject the present application- i.e., whether the present ***method*** claims are directed to a new use for an old composition/compound such that the method is non-obvious over the teachings of the cited prior art. Applicant respectfully submits that the present method claims are clearly patentable based upon this well settled concept in patent law, as presented in detail hereinabove.

For the above reasons, Applicants respectfully assert that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

No fee is due for the presentation of the amendments made herein. A request for continued examination (RCE) is enclosed as is authorization to charge the fee of $405 for the RCE to Deposit Account 04-0838. Please charge any additional fee due or credit any overpayment to Deposit Account No. 04-0838.

Applicant notes that he has specifically requested an interview with Examiner Badio prior to the issuance of an office action and anticipates that the first office action in any event will be a ***non-final*** office action.

If the Examiner believes that further discussion of the present application with the undersigned attorney may materially advance the prosecution of this application, she is cordially requested to telephone the undersigned at the telephone number listed below.

Respectfully submitted,
Coleman Sudol Sapone, P.C.
By: _____

Enc.

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being sent by facsimile transmission to Examiner Barbara Badio in Group Art Unit 1628 of the United States Patent and Trademark Office, at P.O. Box 1450 Alexandria, Virginia 22313-1450" on May 17, 2011.

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Henry D. Coleman